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2021-08-15

Laakso , S M , Myllynen , C , Strbian , D & Atula , S 2021 , ' Comorbidities worsen the prognosis of generalized myasthenia gravis post-thymectomy ' , Journal of the Neurological Sciences , vol. 427 , 117549 . https://doi.org/10.1016/j.jns.2021.117549

http://hdl.handle.net/10138/334377
https://doi.org/10.1016/j.jns.2021.117549

Journal of the Neurological Sciences 427 (2021) 117549

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Comorbidities worsen the prognosis of generalized myasthenia gravis post-thymectomy

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ARTICLE INFO

Keywords:
Myasthenia gravis
Thymectomy
Comorbidity
Prognosis
Neuroimmunological disease
Treatment

ABSTRACT

Background: The effect of comorbidities on the prognosis of myasthenia gravis (MG) remains unclear. In particular, the role of other autoimmune diseases (AD) is controversial.
Methods: In this retrospective single-center cohort study, we investigated 154 consecutive generalized thymectomized MG patients, with a mean follow-up time of 8.6 (±5.0) years post-thymectomy. Comorbidities diagnosed at any timepoint were retrieved from medical records and Charlson comorbidity index (CCI) scores were calculated. Patients were categorized into subgroups MG alone ($n = 45$) and MG with any comorbidity ($n = 109$); the latter was further categorized into MG with other ADs ($n = 33$) and MG with non-AD comorbidities ($n = 76$). The endpoints analyzed were complete stable remission (CSR), minimal need for medications, and need for in-hospital treatments.
Results: CSR was more frequent in MG alone than in MG with any comorbidity group (26.7% vs 8.3%, $p = 0.004$). Minimal need for medication was reached more often in the MG alone than in the MG with non-AD comorbidities group ($p = 0.047$). Need for in-hospital treatments was lower in the MG alone group than in MG patients with any comorbidity ($p = 0.046$). Logistic regression analysis revealed that lower CCI scores increased the likelihood of CSR ($p = 0.033$). Lower CCI scores were more prevalent both in patients with minimal need for medication and in patients who did not need in-hospital treatments ($p < 0.001$).
Conclusions: Patients with generalized MG and comorbidities have a poorer prognosis than patients with MG alone during almost 9 years follow-up after thymectomy. AD comorbidities appeared not to translate into a higher risk compared to other comorbidities.

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction, where exercise-induced and reversible loss of muscle strength are the key clinical features. However, the disease is diverse regarding the range of muscles involved, age at onset, pathological autoantibodies detected, eventual pathological findings of the thymus, and prognosis [1]. Antibodies against the acetylcholine receptor (AChR) are present in 85% of patients with generalized MG, whereas muscle-specific kinase (MuSK) is the target for antibodies in 5% of patients. Rare targets, such as low-density lipoprotein receptor-related protein 4 (LRP4), have also been identified [2]. In early-onset generalized MG, symptoms start before the age of 50, patients are usually women, and thymic hyperplasia is found in 70% of patients, correlating strongly to AChR autoantibody production [3]. Late-onset generalized MG also presents with AChR autoantibodies, but both genders are equally affected and thymic hyperplasia is rare [1]. Thymoma as the inducer of MG has a paraneoplastic nature and explains 10% to 15% of all MG cases [4].

Treatment of MG may include cholinesterase inhibitors, non-specific immunosuppression, and thymectomy in patients <70 years with AChR autoantibodies or a thymoma [5]. In many observational studies, thymectomy is associated with a reduction of immunosuppressive medication, decrease in symptoms and greater chance of complete stable remission (CSR) of also nonthymomatous MG [6,7]. In the only randomized controlled trial performed to date, fewer thymectomized non-thymomatous MG patients required prednisone-sparing immunosuppressants (17% vs 48%) or hospitalization for an

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https://doi.org/10.1016/j.jns.2021.117549
Received 25 January 2021; Received in revised form 15 June 2021; Accepted 16 June 2021
Available online 19 June 2021

exacerbation of MG (9% vs 37%) than patients in the prednisone-only group 3 years after the operation, thus showing a sustained benefit [8].

The prognosis of MG is considered to be generally good and chronic symptoms can be managed with the treatments mentioned above [5]. However, CSR occurs in only 22% of AChR-positive MG patients [9]. Also, MG is classified as refractory in 10% to 20% of patients who do not achieve adequate response, do not tolerate available therapies, or require recurring in-hospital rescue therapies such as intravenous immunoglobulin (IVIG) or plasmapheresis (PLEX) [10]. Younger age at onset, female sex, history of thymoma, and positive MuSK antibodies are features associated with refractory MG [11,12].

Other autoimmune diseases (ADs) are strongly associated with MG. MG patients have a 22% risk of another AD during their lifetime, compared to 9% in an age- and sex-matched control group randomly selected from the MG-free general Swedish population [13]. Thyroiditis, systemic lupus erythematosus, rheumatoid arthritis, type 1 diabetes, Addison's disease, dermato- or polymyositis, and neuromyelitis optica are the ADs most commonly associated with MG [13–17]. Co-occurrence of another AD is more common with early-onset than late-onset MG [17]. Thyroiditis also often co-occurs with the ocular, usually mild form of MG [14,18]. Thymoma-induced MG, on the other hand, is associated with hematological ADs and autoimmune myocarditis [1]. Interestingly, a recent Taiwanese study concluded that patients with or without MG who underwent thymectomy had a higher risk of new onset AD [19]. Currently, non-autoimmune comorbidities, such as type 2 diabetes, hypertension, and coronary diseases, are common in MG due to increased life expectancy and are understandably more common in patients with late-onset MG [20].

The effect of comorbidities on the prognosis of MG and treatment response is still unclear. One study reported that patients with autoimmune comorbidities were at considerable risk for a relapse of MG [21]. In another study, autoimmune thyroid disease did not seem to increase the risk of myasthenic crises or to reduce response to medication [18]. In a Mexican study, response to thymectomy did not differ between MG patients with or without other ADs [22]. One study on 88 MG patients reported that patients with more than two comorbidities, autoimmune or non-autoimmune, had a greater risk for a crisis of MG and a generally poorer outcome [20].

Considering the notable differences in disease severity and pathological profiles in MG, we sought to control these variables by investigating a series of consecutive generalized MG patients with thymectomy and with an extensive follow-up time to determine the effect of comorbidities on the prognosis of generalized MG.

2. Materials and methods

2.1. Data collection

For this retrospective single-center cohort study, our series consisted of consecutive patients with generalized MG who had undergone a thymectomy between 1999 and 2015. The patient data have been characterized in detail by Kauppi et al. [23]. The patients were followed from diagnosis of MG to the last follow-up visit at the neurology outpatient clinic. Data for comorbidities diagnosed at any time point before or after thymectomy were collected from hospital patient medical records, and the number and nature of comorbidities before thymectomy and of those emerging during the post-thymectomy follow-up were determined. Comorbidities were captured only if there was a diagnosis found in the chart, and possible subclinical undiagnosed comorbidities were not searched for. The latest review of the patients' data was performed in April 2020. Neurologists diagnosed MG based on clinical presentation, anti-AChR and anti-MuSK antibody serology tests, and electrophysiological tests (ENMG). The severity of MG was graded using the Myasthenia Gravis Foundation of America Clinical Classification (MGFA) as I to V during review of patient records; MGFA class I means any ocular muscle weakness, class II mild generalized weakness, class III moderate generalized weakness, class IV severe generalized weakness, and class V intubation with or without mechanic ventilation [24].

Clinical parameters of the study were use of immunosuppressive drugs, pyridostigmine dose, discontinuation of all MG medication, need for admission to the intensive care unit (ICU), and need for high-dose intravenous methylprednisolone (IVMP), PLEX, or IVIG treatment. CSR was defined as discontinuation of all medication (including acetylcholinesterase inhibitors such as pyridostigmine) for MG at least 12 months before the last follow-up visit and no evidence of active disease thereafter. Patients classified to have a minimal need of medication were those in CSR or using pyridostigmine as the only medication (maximum 100 mg per day). Need for in-hospital treatments for exacerbations of MG was treatment at ICU or receiving IVMP, PLEX, or IVIG treatment during the follow-up period after thymectomy until the last follow-up visit. Clinical predictors were compared between patients with or without comorbidities. We formed subgroups based on comorbidities. The first subgroups were MG patients without any comorbidities (MG alone) and MG patients with any comorbidity. We then divided the latter subgroup further into patients with MG and other AD and MG patients with comorbidities other than AD (MG with non-AD comorbidity). Patients that had both other ADs and other comorbidities were assigned to the group MG with other AD.

To further investigate the role of comorbidities in MG, we calculated a score for comorbidity by the Charlson comorbidity index (CCI). CCI is a summary measure that estimates risk of death from comorbid diseases and patient age and is widely used by researchers to measure burden of disease. The index considers 17 different comorbid conditions, such as cancer, diabetes, or congestive heart failure. The weight of each condition is estimated by its severity. Of autoimmune diseases, type 1 diabetes, connective tissue diseases, and autoimmune diseases of the liver and kidney are included. Comorbid conditions are assigned a score from one to six points, and weighted scores are summed to provide a summary score or CCI. The higher the summary score, the higher the risk of 1-year mortality [25,26].

The study was approved by the institutional review board of Helsinki University Hospital. According to Finnish law, approval of the ethical committee was not required because the study was based on hospital medical records and included no contact with patients.

2.2. Statistical methods

Statistical analyses were performed with SPSS software version 25 (IBM, New York). Demographic data were described by means and standard deviations (SD) for normally distributed variables and medians and ranges otherwise. We compared continuous variables by the Mann-Whitney *U* test and categorical variables by Fisher's exact test. We used logistic regression analysis for continuous variables. A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Demographics of the study population and prevalence of comorbidities

Of the 154 patients studied, 76 (49.0%) were females. ENMG test was positive in 139 patients (90.3%), AChR antibodies were detected in 130 patients (84.4%), and MuSK antibodies in 1 patient (0.7%). Thymoma was found in 7 patients (4.5%). The mean total follow-up time was 9.6 (±5.3) years and the mean follow-up time from thymectomy to the last follow-up visit was 8.6 (±5.0) years.

Demographic and clinical characteristics of the studied MG subgroups are presented in Table 1. Forty-five patients in the study population had MG alone at the end of follow-up. From the total of 109 patients with any comorbidity, 33 (21.4%) had other ADs and 76 (49.4%) had non-AD comorbidities at the end of follow-up. We included all patients who had other ADs into the MG with other AD group,

Table 1
Demographic parameters of the study subgroups*.

	MG alone	MG with comorbidities**		
		MG with any comorbidity	MG with other AD	MG with non-AD comorbidity
N (% of total group)	45 (29.2%)	109 (70.8%) $p < 0.0001$	33 (21.4%)	76 (49.4%) $p < 0.001$
Female, n (%)	34 (75.6%)	42 (49.4%) $p < 0.0001$	17 (51.5%) $p = 0.033$	25 (32.9%) $p < 0.0001$
Age at diagnosis of MG, mean in years (±SD)	34.4 (±16.8)	54.8 (±14.3) $p < 0.0001$	53.8 (±14.0) $p < 0.0001$	55.2 (±14.2) $p < 0.0001$
Age at thymectomy, mean in years (±SD)	35.1 (±16.8)	56.0 (±14.3) $p < 0.0001$	55.2 (±14.0) $p < 0.0001$	56.8 (±14.3) $p < 0.0001$
Delay between diagnosis and thymectomy, mean in years (±SD)	0.7 (±1.4)	1.2 (±1.6)	1.4 (±1.6) $p = 0.044$	1.1 (±1.3)
MGFA class at the time of diagnosis, n (%)				
I	10 (22.2%)	26 (23.9%)	7 (21.2%)	19 (25.0%)
II	23 (51.1%)	51 (46.8%)	15 (45.5%)	36 (47.4%)
III	10 (22.2%)	26 (23.9%)	9 (27.3%)	17 (22.4%)
IV	0	2 (1.8%)	1 (3.0%)	1 (1.3%)
V	1 (2.2%)	2 (1.8%)	0	2 (2.6%)
Total follow-up time, mean in years (±SD)	8.2 (±5.3)	10.2 (±4.9) $p = 0.026$	12.3 (±4.9) $p = 0.001$	9.3 (±4.7)
Time between thymectomy and the last follow-up visit, mean in years (±SD)	7.3 (±5.0)	9.0 (±4.7) $p = 0.047$	10.9 (±4.7) $p = 0.002$	8.2 (±4.5)

* Study subgroups were formed based on the presence of comorbidities at the end of follow-up. **Patients with both other AD comorbidity and non-AD comorbidity were included in the MG with other AD subgroup. *MG* myasthenia gravis; *AD* autoimmune disease; *MGFA* Myasthenia Gravis Foundation of America; *p*-values for statistically significant differences between MG alone and the other subgroups studied are shown; those not shown were insignificant.

although 23 of these patients also had a non-AD comorbidity. The subgroup analysis showed that patients with MG alone were more often women, and mean age at time of MG diagnosis was clearly lower than in the other subgroups (34.4 [±16.8] years vs 54.8 [±14.3] years in patients with any comorbidity; $P < 0.0001$). MGFA class at time of diagnosis was not significantly different between groups. The follow-up time of the study was longer for patients with comorbidities (8.2 [±5.3] years for MG alone vs 10.2 [±4.9] years for MG with any comorbidities; $p = 0.026$).

The prevalence of comorbidities in the study population is shown in Table 2a. During the post-thymectomy follow-up, there were a total of 39 individual patients diagnosed with altogether 49 new comorbidities, of which 19 were cardiovascular or metabolic or most likely related to these two classes (i.e. sleep apnea, 5 patients). Two patients had MG alone before thymectomy and developed non-AD comorbidities before the end of follow-up. Eleven new diagnoses of an AD were made during the post-thymectomy follow-up, of which ten to patients who had no other diagnoses besides MG at the time of thymectomy. Autoimmune thyroid disease was the most common AD observed at the end of follow-up and accounted for 50% ($n = 20$) of AD cases. Almost half of all patients had two or more of any kind of comorbidities at the end of follow-up ($n = 71$, 46.1%). The median CCI score at the end of follow-up was 2 and the highest score was 6 ($n = 2$) (Table 2b). The MG alone group had 5 patients with CCI score of 2, which is due to the points assigned from age of patient.

Patients with thymoma ($n = 7$) were slightly older at the time of diagnosis than non-thymomatous MG patients ($n = 147$, 57.4 [±16.8] years vs 48.3 [±17.0] years). Two of the patients were female, and mean follow-up time was 7.0 (±5.3) years. None of the thymomatous MG patients had other ADs before thymectomy, but one developed an other-

Table 2
Comorbidities in the study population.

a)

Non-autoimmune comorbidities	Number of patients before thymectomy (% of all patients, $n = 154$)	Number of patients at the end of follow-up (% of all patients, $n = 154$)
Cardiovascular disease	56 (36.4%)	62 (40.3%)
Metabolic disease	24 (15.6%)	30 (19.5%)
Respiratory disease	18 (11.7%)	23 (14.9%)
Cancer	9 (5.8%)	18 (11.7%)
Mental disorder	9 (5.8%)	10 (6.5%)
Other neurological disease	4 (2.6%)	9 (5.8%)
Other diseases	8 (5.2%)	8 (5.2%)
Musculoskeletal disease	1(0.6%)	3 (1.9%)
Hematological disease	1 (0.6%)	2 (1.3%)
Autoimmune comorbidities		
Autoimmune thyroid disease	17 (11.0%)	20 (13.0%)
Rheumatoid arthritis	4 (2.6%)	6 (3.9%)
Ulcerative colitis or Crohn's disease	3 (1.9%)	4 (2.6%)
Psoriasis	2 (1.3%)	4 (2.6%)
Henoch-Schönlein purpura	1 (0.6%)	2 (1.3%)
Primary sclerosing cholangitis	0	1 (0.6%)
Systemic lupus erythematosus	1 (0.6%)	1 (0.6%)
Celiac disease	1 (0.6%)	1 (0.6%)
Polymyalgia rheumatica	0	1 (0.6%)

Prevalence of non-autoimmune and autoimmune comorbidities, shown both before thymectomy (on the left) and at the end of follow-up (on the right). Cardiovascular diseases reported were hypertension, coronary artery disease, cardiac arrhythmia, congenital heart defect, and heart failure. Metabolic diseases were type 2 diabetes, hypercholesterolemia, and gout. Respiratory diseases were asthma, sleep apnea, chronic bronchitis, asbestosis, pulmonary sarcoidosis, chronic respiratory failure. Other neurological diseases were epilepsy, Parkinson's disease, Alzheimer's disease, migraine, trigeminal neuralgia, and transient ischemic attack. Hypertension was the most prevalent single comorbidity ($n = 58$). *MG* myasthenia gravis.

Table 2b

b).

CCI score*	MG alone, n (%, out of 45 patients)	MG with any comorbidity, n (%, out of 109 patients)	MG with other AD, n (%, out of 33 patients)	MG with non-AD comorbidity, n (%, out of 76 patients)
0–1	40 (88.9%)	26 (23.9%)	9 (27.3%)	17 (22.4%)
2–4	5 (11.1%)	69 (63.3%)	20 (60.6%)	49 (64.5%)
5–6	0	14 (12.8%)	4 (12.1%)	10 (13.2%)

*The CCI scores were calculated based on the presence of comorbidities at the end of follow-up. *CCI* Charlson comorbidity index; *MG* myasthenia gravis; *AD* autoimmune disease.

AD during post-thymectomy follow-up.

3.2. Treatment of MG and achievement of CSR in the studied subgroups

The rate of in-hospital treatments for exacerbations of MG during the follow-up period after thymectomy is shown in Table 3. IVMP was given significantly more often to patients with any comorbidities when compared with MG alone (35.8% vs 17.8%; $p = 0.034$). Other ADs as comorbidities were unremarkable. There were no significant differences in postoperative ICU admission, PLEX, or IVIG treatment among any of the studied subgroups.

Immunosuppressive drugs were used more frequently in the MG with any comorbidities group than in the MG alone group at the last follow-up visit (41.3% vs 20.0%; $p = 0.015$). Immunosuppressive drugs prescribed included oral prednisolone (18 patients), azathioprine (36 patients) and methotrexate (4 patients). Again, other ADs as comorbidities were unremarkable. There was no difference in the mean pyridostigmine dose between any of the subgroups.

CSR was significantly more frequent in MG patients without comorbidities as compared with MG patients with any comorbidity (26.7% vs 8.3%; $p = 0.004$). This difference remained when dividing the comorbidities into other ADs (26.7% vs 6.1%; $p = 0.034$) and non-AD comorbidities (26.7% vs 9.2%; $p = 0.018$).

We further performed a binary logistic regression analysis to assess the impact of gender, age at MG diagnosis, and CCI score (independent variables) on the likelihood of achieving CSR. The regression model was statistically significant (χ^2 (3) = 12.848; $p < 0.005$) and correctly classified 85.6% of cases. The model overall explained between 8.1% (Cox and Snell *R* square) and 14.4% (Nagelkerke *R* squared) of the variance in CSR. Only the CCI score made a statistically significant unique contribution to the model, with lower CCI scores increasing the likelihood of reaching CSR ($p = 0.033$) (Table 4). Pearson correlation coefficient for age at MG diagnosis and CCI score at the end of follow-up was very strong ($r = 0.837$, $p < 0.001$).

Table 3
Treatment of myasthenia gravis (MG) and achievement of complete stable remission (CSR) during the post-thymectomy follow-up in the subgroups.

Patients given in-hospital treatments for an exacerbation, n (%)	MG alone	MG with any comorbidity	MG with other AD	MG with non-AD comorbidity
IVMP	8 (17.8%)	39 (35.8%) $p = 0.034$	10 (30.3%)	29 (38.2%) $p = 0.024$
PLEX	2 (4.4%)	15 (13.8%)	5 (15.1%)	10 (13.2%)
IVIG	2 (4.4%)	9 (8.3%)	5 (15.1%)	4 (5.3%)
ICU	3 (6.7%)	15 (13.8%)	4 (12.1%)	11 (14.5%)
Patients in need of in-hospital treatments during the post-thymectomy follow-up, n (%)	12 (26.7%)	49 (45.0%) $p = 0.046$	16 (48.5%)	33 (43.4%)
Immunosuppressive drugs at the last follow-up visit, n (%)	9 (20.0%)	45 (41.3%) $p = 0.015$	13 (39.3%)	32 (42.1%) $p = 0.017$
Pyridostigmine dose at the last follow-up visit, mg, median (range)	225 (40–680)	190 (10–600)	240 (30–600)	180 (10–560)
CSR at the last follow-up visit, n(%) †	12 (26.7%)	9 (8.3%) $p = 0.004$	2 (6.1%) $p = 0.034$	7 (9.2%) $p = 0.018$
Minimal need for medication at the last follow-up visit, n (%) ‡	15 (33.3%)	20 (18.3%)	7 (21.2%)	13 (17.1%) $p = 0.047$

AD autoimmune disease; *IVMP* intravenous methylprednisolone; *PLEX* plasmapheresis; *ICU* intensive care unit; *IVIG* intravenous immunoglobulin. †CSR was defined as discontinuation of all MG medication at least 12 months before the last follow-up visit and no evidence of active disease thereafter. ‡ Minimal need for medication was defined as complete stable remission (CSR) or maximum dose of 100 mg per day of pyridostigmine alone. *p*-values for statistically significant differences between MG alone and the other subgroups studied are shown; those not shown were insignificant.

3.3. Minimal need for medication after thymectomy and need for in-hospital treatments for exacerbations of MG after thymectomy

We next assessed minimal need for medication after thymectomy, defined as CSR or maximum dose of 100 mg per day of pyridostigmine alone. This endpoint was reached significantly more often in the MG alone group than in the MG with non-AD comorbidities group ($p = 0.047$) (Table 3). There were no significant differences between the other subgroups. We used the CCI score to further analyze the effect of comorbidities on this endpoint. The distributions of the CCI score between patients with minimal need for medication and patients with more medications were significantly different in the entire study population (Mann-Whitney *U* test; $p < 0.001$) (Fig. 1a).

Need for in-hospital treatments for exacerbations of MG during the post-thymectomy follow-up was also analyzed. There was a significant difference between MG alone and MG with any comorbidity subgroups regarding this endpoint ($p = 0.046$) (Table 3). Dividing the comorbidities into other ADs and non-AD comorbidities did not yield a significant difference compared to the MG alone group. The distributions of the CCI score between patients who required in-hospital treatments and patients managed with regular outpatient care in the entire study population were also significantly different (Mann-Whitney *U* test; $p < 0.001$) (Fig. 1b).

Patients with thymomatous MG ($n = 7$) did not reach CSR, but the number of patients in need of in-hospital treatments was similar to non-thymomatous cases (57.1% vs 38.7%).

4. Discussion

This study shows that patients with generalized MG who have comorbidities are less likely to achieve CSR during the post-thymectomy follow-up than patients with MG alone, and that the effect is similar with both autoimmune and non-autoimmune comorbidities. We used CCI score to quantify the overall burden of comorbidities. CCI score in a logistic-regression model revealed a significant inverse correlation to achievement of CSR when known confounding factors of age at diagnosis and gender [11] were considered. The percentage of patients achieving CSR was significantly higher in the MG alone group. The prevalence of other ADs (21.3%) and the range of ADs present were consistent with previous reports [1,13,20,22], with a preponderance of autoimmune thyroid disease. Non-AD comorbidities were common, with the most common comorbidity of hypertension diagnosed in 37.7% of all patients in this study. Minimal need for medication at the end of follow-up was significantly more likely in the MG alone group than in patients with non-AD comorbidities and likewise for those with low CCI scores. Need of in-hospital treatments for exacerbations of MG was more common in patients with any comorbidity than in patients with MG alone and likewise for those with high CCI scores.

Our results are consistent with a previous study that revealed an association between comorbidities with poorer prognosis regarding the

Table 4
Logistic regression model for complete stable remission (CSR).

	OR	95% CI	*p*-value
Gender	1.44	0.46–4.51	0.533
Age at diagnosis	1.00	0.95–1.06	0.785
CCI score	0.51	0.28–0.95	0.033*

OR odds ratio; *CI* confidence interval. *Statistically significant at the $p < 0.05$ level.

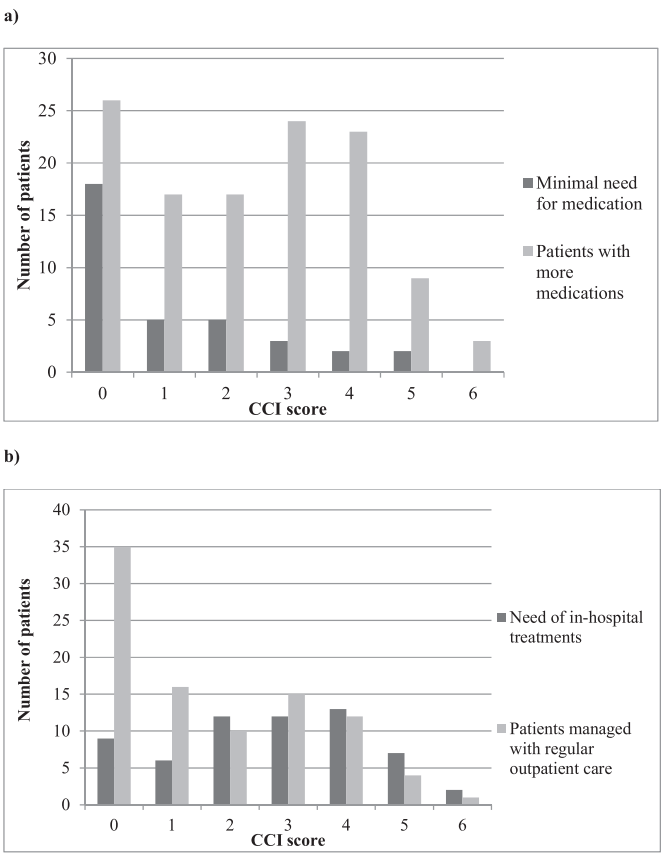

Fig. 1. a) Patients with minimal need for medication at the end of follow-up and patients that were prescribed more medications distributed by the Charlson comorbidity index (CCI) score ($n = 154$). Minimal need for medication was defined as complete stable remission (CSR) or maximum dose of 100 mg per day of pyridostigmine alone. The distributions of the CCI score were significantly different ($p < 0.001$; Mann-Whitney U test). **b)** Patients that need in-hospital treatments in the post-thymectomy follow-up and patients managed with regular outpatient care distributed by the CCI score (n = 154). The distributions of the CCI score were significantly different ($p < 0.001$; Mann-Whitney U test).

need for in-hospital treatments for MG [20]. Other comorbid ADs when compared with non-AD comorbidities were unremarkable in terms of prognosis. This observation is in contrast to Wang et al. 2017 but consistent with Kubiszeska et al. 2016 [18,21]. Our study addressed the issue of numerous clinical variables that affect the severity of MG by focusing on generalized MG that the clinician had assessed to be severe enough to warrant thymectomy. Generalisability of our results into patients not perceived to benefit from thymectomy is therefore questionable. Thymectomy as the starting point of the study population selection might also explain differences to previous studies. However, a similar study approach and a comparative sample size was used by Téllez-Zenteno et al. 2004 [22] with contrasting results, which may be due to differences in patient selection.

Our study had a substantial mean follow-up time of 8.6 years (±5.0) after thymectomy, which increases the likelihood of capturing all relevant diagnoses even when using retrospective patient record review as the method of data collection. MG treatment is centralized at our hospital. MG exacerbations requiring in-hospital treatment are directed in Finland to public hospitals that are all in the same electronic patient record system in our hospital district. Comorbidities can also be diagnosed and treated in the private sector but are still recorded in patient records, especially for MG patients, as all medications must be considered when assessing the causes of possible disease progression. All patients in the study population were under regular follow-up at the outpatient clinic, which increases the reliability of the data. We did not however search for subclinical undiagnosed autoimmune diseases, which is a limitation of the study. Studying a consecutive series of MG patients undergoing thymectomy further increases the relevance of our data in describing the patient population at hand.

A limitation in our study approach is that patients with MG alone were significantly younger than patients with comorbidities. Younger age at thymectomy might be a confounding factor for better response to the operation, because thymic hyperplasia and subsequent higher production of AChR antibodies is more prevalent in patients under the age of 50, and thymic involution with age correlates with lowering numbers of germinal centers in the thymus [3]. We sought to confirm the findings of subgroup analysis by using the CCI score for the entire study population. However, this limitation remains as age is also a factor in the CCI score, and there was a significant correlation between age at MG onset and CCI score at the end of follow-up. Interestingly, younger age at disease onset in itself is associated with the risk of refractory MG [11,12]. Therefore, based on our results, it can be hypothesized that comorbidities could outweigh age at disease onset as a risk factor for refractory MG.

Another point of concern is, whether immunosuppressive treatments for MG, especially corticosteroids, have contributed to the emergence of new non-AD comorbidities, and therefore form a confounding factor in the study. Our approach of classifying patients into subgroups MG alone and MG with comorbidities was however not substantially affected by this, because only two out of 76 patients entered the subgroup MG with non-AD comorbidities during the post-thymectomy follow-up.

The method of retrospective data collection and moderate sample size ($n = 154$) are also limitations in this study. We wanted to study especially the effect of having other ADs in this setting, and therefore included 23 patients into the MG with other AD group that also had non-AD comorbidities. Non-AD comorbidities could therefore also affect the results of the MG with other AD group. The rationale for our choice was to achieve a reasonable size of the subgroup and to determine if having other ADs in itself would change the prognosis. Our results indicate that other ADs do not substantially change the prognosis of MG compared to the effect that non-AD comorbidities have, as these subgroups had similar results regardless of the clinical parameters used. It is however of interest that thymectomy did not seem to protect the MG patients from developing new ADs, nor lessen the effect of other AD comorbidities on the prognosis. Extra-thymic plasma cells are thought to contribute to persistent antibody generation after thymectomy, which is most likely of relevance here [27].

MGFA score at diagnosis was not significantly different in the subgroups. This highlights the differences in outcome measures emerging later in follow-up and with the short time interval between diagnosis and thymectomy, most likely in the post-thymectomy period. However, it should be noted that the follow-up time of patients both in total and after thymectomy was shorter for patients with MG alone, and this might affect our results.

Further studies on the exact comorbidities affecting the prognosis of generalized MG are needed. Larger study samples would be beneficial. A nationwide study is warranted considering the increasing but still quite low prevalence of MG, recently estimated to be 29/100,000 in Finland based on data from drug reimbursement rights [28]. Whether indications for thymectomy should be different for patients with comorbidities cannot be answered based on our study, and this should be addressed further. The impact of comorbidities on the prognosis of MuSK autoantibody-positive MG patients and those with thymoma, both groups associated with a higher risk of refractory MG [5], remain outside the scope of this study due to the low patient numbers and should be studied further.

In conclusion, our study shows that patients with generalized MG and comorbidities have a poorer prognosis after thymectomy than patients with MG alone, and this effect prevails after almost 9 years of follow-up. AD comorbidities do not seem to be a higher risk compared to

other comorbidities. Thymectomy is a beneficial treatment for generalized MG, but not sufficient to limit disease activity especially in patients with comorbidities. Clinical decision-making guidelines for the treatment of MG emphasize considering disease heterogeneity [29]; Our results indicate that comorbidities have a significant effect on the presence of symptoms of MG, and should be evaluated along with other factors known to affect the severity of MG.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Competing Interest

The authors have nothing to disclose related to this manuscript.

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